	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	514	(glucagon-like adj peptide) or glp-1 or glp-2	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:23			0
2	BRS	L2	2010	lipophilic adj (substituent or group)	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:26			0
3	BRS	L3	18	1 same 2	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:35			0
4	BRS	L4	12351	(fatty adj acid) same (amino)	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:49			0
5	BRS	L5	6	1 same 4	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:37			0
6	BRS	L6	344	spacer same ((succinic adj acid) or glu or asp)	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:39			0
7	BRS	L7	4	3 same 6	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:39			0
8	BRS	L8	0	5 same 6	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:40			0
9	BRS	L9	1039	tetradecanoyl	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:41			0
10	BRS	L10	8	1 same 9	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:42			0
11	BRS	L11	174623	fatty adj acid	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:50			0
12	BRS	L12	34	1 same 11	USPAT; US-PGPUB; EPO; DERWENT	2002/05/21 07:51			0

> d his

(FILE 'HOME' ENTERED AT 07:57:13 ON 21 MAY 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
07:57:48 ON 21 MAY 2002
L1 9389 S (GLUCAGON-LIKE PEPTIDE) OR GLP-1 OR GLP-2
L2 730112 S LIPOPHILIC OR (FATTY ACID)
L3 322 S L1 (P) L2
L4 13 S L3 (P) SUBSTIT?
L5 8 DUPLICATE REMOVE L4 (5 DUPLICATES REMOVED)
L6 1567656 S SPACER OR LINK?
L7 221176 S (SUCCINIC ACID) OR GLU OR ASP OR LYS OR GLY-LYS
L8 15810 S L6 (P) L7
L9 13606 S TETRADECANOYL
L10 8 S L1 (P) L9
L11 4 DUPLICATE REMOVE L10 L10\ (4 DUPLICATES REMOVED)
L12 4 S L11 NOT L5
L13 30 S L3 AND L6
L14 12 DUPLICATE REMOVE L13 (18 DUPLICATES REMOVED)
L15 12 S L14 NOT (L5 OR L11)

=> log y

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FILE 'HOME' ENTERED AT 07:57:13 ON 21 MAY 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 07:57:48 ON 21 MAY 2002

FILE 'CAPLUS' ENTERED AT 07:57:48 ON 21 MAY 2002
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FILE 'BIOSIS' ENTERED AT 07:57:48 ON 21 MAY 2002
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FILE 'EMBASE' ENTERED AT 07:57:48 ON 21 MAY 2002
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FILE 'SCISEARCH' ENTERED AT 07:57:48 ON 21 MAY 2002
COPYRIGHT (C) 2002 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 07:57:48 ON 21 MAY 2002

=> s (glucagon-like peptide) OR GLP-1 OR GLP-2
L1        9389 (GLUCAGON-LIKE PEPTIDE) OR GLP-1 OR GLP-2

=> s lipophilic or (fatty acid)
L2      730112 LIPOPHILIC OR (FATTY ACID)

=> s l1 (p) l2
L3         322 L1 (P) L2

=> s l3 (p) substit?
L4          13 L3 (P) SUBSTIT?

=> duplicate remove l4
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L4
L5             8 DUPLICATE REMOVE L4 (5 DUPLICATES REMOVED)

=> d l5 1-8 ibib abs

L5   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS         DUPLICATE 1
ACCESSION NUMBER:         2001:721487  CAPLUS
DOCUMENT NUMBER:          135:273221
TITLE:                    Preparation of lipophilic human glucagon-like
                          peptide-1 derivatives with protracted action profiles
INVENTOR(S):              Knudsen, Liselotte; Huusfeldt, Per Olaf; Nielsen, Per
                          Franklin; Kaarsholm, Niels C.; Olsen, Helle Birk;
                          Bjorn, Soren Erik; Pedersen, Freddy Zimmerdahl;
                          Madsen, Kjeld
PATENT ASSIGNEE(S):       Novo Nordisk A/s, Den.
SOURCE:                   U.S., 136 pp., Cont.-in-part of U.S. Ser. No. 38,432,
                          abandoned.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   11
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     US 6268343         B1   20010731       US 1999-258750   19990226
     WO 9808871         A1   19980305       WO 1997-DK340    19970822
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
```

UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, [redacted] UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

JP 2001011095	A2	20010116	JP 2000-152778	19970822
ZA 9901571	A	19990902	ZA 1999-1571	19990226
US 2001011071	A1	20010802	US 1999-398111	19990916
US 2002025933	A1	20020228	US 2001-908534	20010718

PRIORITY APPLN. INFO.:

DK 1996-931	A	19960830
DK 1996-1259	A	19961108
DK 1996-1470	A	19961220
US 1997-36255P	P	19970124
US 1997-36226P	P	19970125
WO 1997-DK340	A2	19970822
US 1997-918810	B2	19970826
DK 1998-263	A	19980227
DK 1998-264	A	19980227
DK 1998-268	A	19980227
DK 1998-272	A	19980227
DK 1998-274	A	19980227
US 1998-38432	B2	19980311
DK 1998-508	A	19980408
DK 1998-509	A	19980408
US 1998-82478P	P	19980421
US 1998-82480P	P	19980421
US 1998-84357P	P	19980421
US 1998-82802P	P	19980423
US 1997-35905P	P	19970124
JP 1998-511183	A3	19970822
US 1997-922200	B2	19970902
DK 1998-271	A	19980227
US 1998-78422P	P	19980318
US 1998-82479P	P	19980421
US 1998-85789P	P	19980518
US 1999-258187	B1	19990225
US 1999-258750	A2	19990226
US 1999-265141	A2	19990308

OTHER SOURCE(S): MARPAT 135:273221

AB The present invention relates to human ***glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) derivs. having a ***lipophilic*** ***substituent*** , compns. contg. these derivs., and to methods for their prepn. A claimed compd. is His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly. Thus, coupling of ***GLP*** - ***1*** (7-37)-OH with Me(CH2)12CO-Glu(OSu)-OCMe3 (Su = succinimidyl) (prepn. given), followed by deesterification with CF3CO2H and chromatog. purifn. gave 8% bis-adduct Lys[Me(CH2)12CO-.gamma.-Glu]26,34- ***GLP*** - ***1*** (7-37)-OH. Several prepd. ***lipophilic*** ***GLP*** - ***1*** analogs were tested for protracted plasma concn. in pigs and were found to be much more persistent than ***GLP*** - ***1*** (7-37). In addn., the time of peak plasma concn. was found to vary within wide limits depending on the particular ***lipophilic*** ***GLP*** - ***1*** deriv. selected. The efficacy of several prepd. derivs. was tested by stimulation of cAMP in a cell line expressing cloned human ***GLP*** - ***1*** receptor.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:566665 CAPLUS

DOCUMENT NUMBER: 135:122756

TITLE: Preparation of lipophilic human glucagon-like peptide-1 derivatives with protracted action profiles

INVENTOR(S): Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf; Nielsen, Per Franklin; Kaarsholm, Niels C.; Olsen, Helle Birk; Bjorn, Soren Erik; Pedersen, Freddy Zimmerdahl; Madsen, Kjeld

PATENT ASSIGNEE(S): Den.

SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S. Ser. No. 265,141.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001011071	A1	20010802	US 1999-398111	19990916
WO 9808871	A1	19980305	WO 1997-DK340	19970822
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
JP 2001011095	A2	20010116	JP 2000-152778	19970822
US 6268343	B1	20010731	US 1999-258750	19990226
US 6384016	B1	20020507	US 1999-265141	19990308
US 2002025933	A1	20020228	US 2001-908534	20010718

PRIORITY APPLN. INFO.:

DK 1996-931	A	19960830
DK 1996-1259	A	19961108
DK 1996-1470	A	19961220
US 1997-36255P	P	19970124
US 1997-36226P	P	19970125
US 1998-84357P	P	19970822
WO 1997-DK340	W	19970822
US 1997-918810	B2	19970826
DK 1998-263	A	19980227
DK 1998-264	A	19980227
DK 1998-268	A	19980227
US 1998-38432	B2	19980311
US 1998-78422P	P	19980318
US 1998-82478P	P	19980421
US 1998-82479P	P	19980421
US 1998-82480P	P	19980421
US 1998-82802P	P	19980423
US 1999-258750	A2	19990226
US 1999-265141	A2	19990308
US 1997-35905P	P	19970124
JP 1998-511183	A3	19970822
US 1997-922200	B2	19970902
DK 1998-271	A	19980227
DK 1998-272	A	19980227
DK 1998-274	A	19980227
EP 1998-610006	A	19980313
DK 1998-508	A	19980408
DK 1998-509	A	19980408
US 1998-85789P	P	19980518
US 1999-258187	B1	19990225

OTHER SOURCE(S): MARPAT 135:122756

AB The present invention relates to pharmaceutical compns. comprising ***lipophilic*** human ***glucagon*** - ***like*** ***peptide***-1 (***GLP*** - ***1***) derivs. having a ***lipophilic*** ***substituent*** and a surfactant. Thus, coupling of ***GLP*** - ***1*** (7-37)-OH with Me(CH2)12CO-Glu(OSu)-OCMe3 (Su = succinimidyl) (prepn. given), followed by deesterification with CF3CO2H and chromatog. purifn. gave 8% bis-adduct Lys[Me(CH2)12CO-.gamma.-Glu]26,34- ***GLP*** - ***1*** (7-37)-OH. Several prepd. ***lipophilic*** ***GLP*** - ***1*** analogs were tested for protracted plasma concn. in pigs and were found to be much more persistent than ***GLP*** - ***1*** (7-37). In addn., the time of peak plasma concn. was found to vary within wide limits depending on the particular ***lipophilic*** ***GLP*** - ***1*** deriv. selected. The efficacy of several prepd. derivs. was tested by stimulation of cAMP in a cell line expressing cloned human ***GLP*** - ***1*** receptor.

L5 ANSWER 3 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000256912 MEDLINE
DOCUMENT NUMBER: 20256912 PubMed ID: 10794683
TITLE: Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily

administration.
AUTHOR: Knudsen L B; [redacted]elsen P F; Huusfeldt P O; Johan[redacted]n N L; Madsen K; Pedersen F Z; Thogersen H; Wilken M; Agerso H
CORPORATE SOURCE: Department of Molecular Pharmacology, Health Care Discovery and Preclinical Development, Novo Nordisk A/S, Novo Park, DK-2760 Maaloev, Denmark.. lbkn@novo.dk
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2000 May 4) 43 (9) 1664-9. Journal code: J0F; 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000629

AB A series of very potent derivatives of the 30-amino acid peptide hormone ***glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) is described. The compounds were all derivatized with ***fatty*** ***acids*** in order to protract their action by facilitating binding to serum albumin. ***GLP*** - ***1*** had a potency (EC(50)) of 55 pM for the cloned human ***GLP*** - ***1*** receptor. Many of the compounds had similar or even higher potencies, despite quite large ***substituents*** . All compounds derivatized with ***fatty*** ***acids*** equal to or longer than 12 carbon atoms were very protracted compared to ***GLP*** - ***1*** and thus seem suitable for once daily administration to type 2 diabetic patients. A structure-activity relationship was obtained. ***GLP*** - ***1*** could be derivatized with linear ***fatty*** ***acids*** up to the length of 16 carbon atoms, sometimes longer, almost anywhere in the C-terminal part without considerable loss of potency. Derivatization with two ***fatty*** ***acid*** ***substituents*** led to a considerable loss of potency. A structure-activity relationship on derivatization of specific amino acids generally was obtained. It was found that the longer the ***fatty*** ***acid*** , the more potency was lost. Simultaneous modification of the N-terminus (in order to obtain better metabolic stability) interfered with ***fatty*** ***acid*** derivatization and led to loss of potency.

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:566077 CAPLUS
DOCUMENT NUMBER: 131:194808
TITLE: GLP-1 derivatives of GLP-1 and exendin with a protracted profile of action
INVENTOR(S): Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf; Nielsen, Per Franklin; Madsen, Kjeld
PATENT ASSIGNEE(S): Novo Nordisk A/s, Den.
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943708	A1	19990902	WO 1999-DK86	19990225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9932477	A1	19990915	AU 1999-32477	19990225
EP 1056775	A1	20001206	EP 1999-936077	19990225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
ZA 9901571	A	19990902	ZA 1999-1571	19990226
US 2001047084	A1	20011129	US 2001-886311	20010621

PRIORITY APPLN. INFO.: DK 1998-274 A 19980227

US 1998-84357P P 19980505
WO 1999-DK86 W 19990225
US 1999-312177 B1 19990514

AB The present invention relates to derivs. exendin and of ***GLP*** - ***1*** (7-C), wherein C is 35 or 36, which derivs. have just one ***lipophilic*** ***substituent*** which is attached to the C-terminal amino acid residue. The derivs. have a protracted action relative to ***GLP*** - ***1*** (7-37) and are useful for treating insulin-dependent and noninsulin-dependent diabetes mellitus. The derivs. of the invention can be combined with other antidiabetics or oral hypoglycemic agents. Pharmaceutical formulations contg. the derivs. of the invention are also claimed.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:566075 CAPLUS
DOCUMENT NUMBER: 131:200093
TITLE: Preparation of GLP-1 analogs for treatment of obesity and non-insulin dependent diabetes mellitus
INVENTOR(S): Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf; Nielsen, Per Franklin; Pedersen, Freddy Zimmerdahl
PATENT ASSIGNEE(S): Novo Nordisk A/s, Den.
SOURCE: PCT Int. Appl., 270 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943706	A1	19990902	WO 1999-DK82	19990225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9926106	A1	19990915	AU 1999-26106	19990225
EP 1060191	A1	20001220	EP 1999-906076	19990225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, FI, RO				
ZA 9901569	A	19990827	ZA 1999-1569	19990226
ZA 9901570	A	19990902	ZA 1999-1570	19990226

PRIORITY APPLN. INFO.: DK 1998-268 A 19980227
WO 1999-DK82 W 19990225

OTHER SOURCE(S): MARPAT 131:200093

AB ***GLP*** - ***1*** analog derivs. His-Xaa8-Xaa9-Gly-Xaa11-Phe-Thr-Xaa14-Asp-Xaa16-Xaa17-Xaa18-Xaa19-Xaa20-Xaa21-Xaa22-Xaa23-Xaa24-Xaa25-Xaa26-Xaa27-Phe-Ile-Xaa30-Xaa31-Xaa32-Xaa33-Xaa34-Xaa35-Xaa36-Xaa37-Xaa38-Xaa39-Xaa40-Xaa41-Xaa42-Xaa43-Xaa44-Xaa45 [Xaa represents an amino acid residue, e.g., Xaa8, Xaa25, Xaa30 = Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, Lys; Xaa9, Xaa21, Xaa27 = Glu, Asp, Lys; Xaa11 = Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, Lys; Xaa14, Xaa17, Xaa18 = Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, Lys] having a ***lipophilic*** ***substituent*** were prepd. for the treatment of obesity and non-insulin dependent diabetes mellitus. Thus, Arg26-34,Lys36[N.epsilon.-[.gamma.-glutamyl(N.alpha.-hexadecanoyl)]] ***GLP*** - ***1*** (7-36)-OH was prepd. via reaction of Arg26-34,Lys36 ***GLP*** - ***1*** (7-36)-OH with Pal-Glu(ONSu)-But (Pal = hexadecanoyl, NSU = succinimide residue). The synthesized compds. have a protracted profile of action relative to ***GLP*** - ***1*** (7-37).

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:566074 CAPLUS
DOCUMENT NUMBER: 131:194807
TITLE: Insulinotropic N-terminally truncated GLP-1 lipophilic

derivatives with protracted action
INVENTOR(S): Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf
PATENT ASSIGNEE(S): Novo Nordisk A/s, Den.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943705	A1	19990902	WO 1999-DK81	19990225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9926105	A1	19990915	AU 1999-26105	19990225
EP 1056774	A1	20001206	EP 1999-906075	19990225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002508162	T2	20020319	JP 2000-533455	19990225

PRIORITY APPLN. INFO.: DK 1998-264 A 19980227
DK 1998-509 A 19980408
WO 1999-DK81 W 19990225
OTHER SOURCE(S): MARPAT 131:194807
AB The present invention relates to N-terminally truncated derivs. of human ***glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) and analogs thereof having a protracted profile of action, as well as the use of such derivs. in pharmaceutical compns. for the treatment of obesity, insulin dependent or non-insulin dependent diabetes mellitus. The ***GLP*** - ***1*** derivs. have a ***lipophilic*** ***substituent*** attached to at least one amino acid residue.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:163616 CAPLUS
DOCUMENT NUMBER: 128:244341
TITLE: Preparation of lipophilic human glucagon-like peptide-1 derivatives with protracted action profiles
INVENTOR(S): Knudsen, Liselotte Bjerre; Sorensen, Per Olaf; Nielsen, Per Franklin
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; Knudsen, Liselotte Bjerre; Sorensen, Per Olaf; Nielsen, Per Franklin
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808871	A1	19980305	WO 1997-DK340	19970822
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9738478	A1	19980319	AU 1997-38478	19970822
AU 732957	B2	20010503		
EP 944648	A1	19990929	EP 1997-935509	19970822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
CN 1232470	A	19991020	CN 1997-198413	19970822

BR 9711437	A	20000118	BR 1997-11437	19970822
JP 2000500505	T2	20000118	JP 1998-511183	19970822
JP 3149958	B2	20010326		
JP 2001011095	A2	20010116	JP 2000-152778	19970822
NO 9900950	A	19990428	NO 1999-950	19990226
US 6268343	B1	20010731	US 1999-258750	19990226
KR 2000035964	A	20000626	KR 1999-701750	19990302
US 2001011071	A1	20010802	US 1999-398111	19990916
US 2002025933	A1	20020228	US 2001-908534	20010718

PRIORITY APPLN. INFO.:

DK 1996-931	A	19960830
DK 1996-1259	A	19961108
DK 1996-1470	A	19961220
US 1997-35905P	P	19970124
US 1997-36255P	P	19970124
US 1997-36226P	P	19970125
JP 1998-511183	A3	19970822
WO 1997-DK340	W	19970822
US 1997-918810	B2	19970826
US 1997-922200	B2	19970902
DK 1998-263	A	19980227
DK 1998-264	A	19980227
DK 1998-268	A	19980227
DK 1998-271	A	19980227
DK 1998-272	A	19980227
DK 1998-274	A	19980227
US 1998-38432	B2	19980311
US 1998-78422P	P	19980318
DK 1998-508	A	19980408
DK 1998-509	A	19980408
US 1998-82478P	P	19980421
US 1998-82479P	P	19980421
US 1998-82480P	P	19980421
US 1998-84357P	P	19980421
US 1998-82802P	P	19980423
US 1998-85789P	P	19980518
US 1999-258187	B1	19990225
US 1999-258750	A2	19990226
US 1999-265141	A2	19990308

AB ***Lipophilic*** human ***glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) derivs. and analogs thereof having a ***lipophilic*** ***substituent*** have interesting pharmacol. properties, in particular they have a more protracted profile of action than ***GLP*** - ***1*** (7-37). Thus, coupling of ***GLP*** - ***1*** (7-37)-OH with Me(CH2)12CO-Glu(OSu)-OCMe3 (Su = succinimidyl) (prepn. given), followed by deesterification with CF3CO2H and chromatog. purifn. gave 8% bis-adduct Lys[Me(CH2)12CO-.gamma.-Glu]26,34- ***GLP*** - ***1*** (7-37)-OH (NNC 90-1167). Several prepd. ***lipophilic*** ***GLP*** - ***1*** analogs were tested for protracted plasma concn. in pigs and were found to be much more persistent than ***GLP*** - ***1*** (7-37). In addn., the time of peak plasma concn. was found to vary within wide limits depending on the particular ***lipophilic*** ***GLP*** - ***1*** deriv. selected. The efficacy of several prepd. derivs. was tested by stimulation of cAMP in a cell line expressing cloned human ***GLP*** - ***1*** receptor.

L5 ANSWER 8 OF 8 EMBASE

ACCESSION NUMBER: 95148057 EMBASE
DOCUMENT NUMBER: 1995148057

TITLE: Glucagon receptors: From genetic structure and expression to effector coupling and biological responses.

AUTHOR: Christophe J.
CORPORATE SOURCE: Department of Experimental Surgery, Medical School, Universite Libre, 40, Avenue J. Wybran,B-1070 Brussels, Belgium

SOURCE: Biochimica et Biophysica Acta - Reviews on Biomembranes, (1995) 1241/1 (45-57).
ISSN: 0304-4157 CODEN: RVBMA3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
048 Gastroenterology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB The 1455 bp rat hepatic glucagon receptor ORF encodes 485 amino acids for a G-protein coupled protein with 7 transmembrane (TM) segments. The deduced amino acid sequence shows 42% identity with the rat ***GLP*** - ***1*** receptor. Transfection of this receptor into COSGs1 cells allows selective glucagon binding and adenylyl cyclase stimulation. It now appears that the rat glucagon receptor gene contains 12 exons, 7 of which code for the TM domain. The gene is transcribed into several pre-mRNAs, variously shortened at the 5' end. One mature intronless mRNA, after the splicing out of the 11 introns, is translated into the functional glucagon receptor. We detected by PCR the apparent expression of the same glucagon receptor in rat liver, heart, islets (.beta. cells?), stomach, kidney and adipocytes, suggesting that one gene allows the expression of only one type of glucagon receptor product, in terms of amino acid sequence. To further analyze the structure-activity relationship of this important yet strictly localized receptor four lines of research are now obvious: (1) To examine the bearing of posttranslational processing by glycosylation, phosphorylation and palmitoylation. (2) The DNA encoding the glucagon receptor being now stably transfected in CHO cells, this will hopefully allow to identify, at the atomic level, the interaction of glucagon with the receptor-effector complex. Such a transfected receptor, well expressed and coupled to adenylate cyclase, can indeed serve as reference when testing plasmids with partial deletions or point mutations (to alter charges), and chimeric constructions (where a fragment of the glucagon receptor is ***substituted*** by the corresponding fragment of a parent receptor, e.g., the tGLP-1 receptor). Mutagenesis of extracellular Asn and Cys residues will reveal the importance of glycosylation and disulfide bridges as prerequisites for receptor function. This evaluation will probably require the use of specific antibodies to see whether a given mutation is not responsible for a mere three-dimensional delocalization and general instability (inactivity) of the receptor synthesized by CHO cells. The binding and functional data collected will not only reveal specific roles for each extra- and intracellular domain of the receptor, they will also indicate how the side chains of residues His1, Gly4, Asp9, Lys12 and Ser16 in glucagon are sterically involved in effector coupling, giving clues in our search for pharmacologically valid analogs. (3) Within the first 104 bp of the 5'-flanking region [91], the TGAGCTCA sequence starting at position - 96 is similar to the consensus sequence TGACGTCA for CRE, and the ACCCAGGC sequence starting at position -50 could be related to the consensus sequence CCCCAGGC for factor AP-2 (that responds to both PKC and PKA). It is important to evaluate the regulation of receptor mRNA transcription with a full characterization (primary DNA sequence, placement, spacing, multiplicity) of regions of promoter sites that contain cis-acting enhancers, such as cAMP-responsive element CRE and tissue-specific elements. These elements could be regulated positively or negatively by trans-acting transcription factors and cofactors reacting to either cAMP (via protein-protein recognition with the C subunit of PKA), phosphorylation, hormones (corticosterone, insulin) or nutrients (glucose, polyunsaturated ***fatty*** ***acids***). Expression assays and transgenic mouse technology could be used to identify these gene regulatory elements and the cell-specific transcription factors that control the limited tissue distribution of this receptor. (4) Appropriate primers will allow a quantitative PCR assay of mRNA levels for glucagon receptors, under various pathological conditions. For instance, in congenital obesity or hypertension in rodents, a change in receptor number in the tissues may reflect alterations in transcription rate and/or mRNA stability. Besides, a precise cellular localization of the receptor mRNA, by in situ hybridization procedures, could delineate whether .beta. and .delta. cells are capable of expressing glucagon receptors and of modulating this synthesis, in response to glucagon secreted by .alpha. cells in the same islets.

=> d his

(FILE 'HOME' ENTERED AT 07:57:13 ON 21 MAY 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 07:57:48 ON 21 MAY 2002
L1 9389 S (GLUCAGON-LIKE PEPTIDE) OR GLP-1 OR GLP-2
L2 730112 S LIPOPHILIC OR (FATTY ACID)

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L3          322 S L1 (P) L2
L4           13 S L3 (P) SUBSTIT?
L5            8 DUPLICATE REMOVE L4 (5 DUPLICATES REMOVED)

=> s spacer or link?
L6      1567656 SPACER OR LINK?

=> s (succinic acid) or glu or asp or lys or gly-lys
L7       221176 (SUCCINIC ACID) OR GLU OR ASP OR LYS OR GLY-LYS

=> s l6 (p) l7
L8        15810 L6 (P) L7

=> s tetradecanoyl
L9        13606 TETRADECANOYL

=> s l1 (p) l9
L10           8 L1 (P) L9

=> duplicate remove l10\
ENTER L# LIST OR (END):l10
PROCESSING COMPLETED FOR L10
L11           4 DUPLICATE REMOVE L10 L10\ (4 DUPLICATES REMOVED)

=> s l11 not l5
L12           4 L11 NOT L5

=> d l11 1-4 ibib abs

L11  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         1999:565944  CAPLUS
DOCUMENT NUMBER:          131:189728
TITLE:                    GLP-2 derivatives with helix-content exceeding 25 %,
                          forming partially structured micellar-like aggregates
INVENTOR(S):              Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf;
                          Nielsen, Per Franklin; Kaarsholm, Niels C.; Olsen,
                          Helle Birk; Thim, Lars; Bjorn, Soren Erik
PATENT ASSIGNEE(S):       Novo Nordisk A/s, Den.
SOURCE:                   PCT Int. Appl., 24 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   11
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 9943361         A1   19990902       WO 1999-DK80     19990225
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9927128         A1   19990915       AU 1999-27128    19990225
     EP 1060192         A2   20001220       EP 1999-907325   19990225
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
     JP 2002504527      T2   20020212       JP 2000-533156   19990225
     US 2002025933      A1   20020228       US 2001-908534   20010718
PRIORITY APPLN. INFO.:                  DK 1998-271      A  19980227
                                        DK 1996-931      A  19960830
                                        DK 1996-1259     A  19961108
                                        US 1997-35905P   P  19970124
                                        US 1997-36226P   P  19970125
                                        US 1997-922200   B2 19970902
                                        US 1998-85789P   P  19980518
                                        US 1999-258187   B1 19990225
                                        WO 1999-DK80     W  19990225
OTHER SOURCE(S):          MARPAT 131:189728
AB   The present invention relates to a pharmaceutical compn. comprising a
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GLP - ***2*** deriv. of improved soly. and/or stability, and to a method for improving the soly. and/or stability of ***GLP*** - ***2*** or a fragment or an analog thereof. Lys30[N.epsilon.-[.gamma.-glutamyl(N.alpha.- ***tetradecanoyl***)]]hGLP-2 was prepd. from hGLP-2-OH, EDPA, NMP and Myr-Glu(ONSu)-OBu-tert.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:163617 CAPLUS
DOCUMENT NUMBER: 128:230696
TITLE: Preparation of lipophilic derivatives of human glucagon-like peptide-2 (hGLP-2)
INVENTOR(S): Knudsen, Liselotte Bjerre; Sorensen, Per Olaf; Nielsen, Per Franklin
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; Knudsen, Liselotte Bjerre; Sorensen, Per Olaf; Nielsen, Per Franklin
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808872	A1	19980305	WO 1997-DK360	19970901
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
JP 2001011095	A2	20010116	JP 2000-152778	19970822
AU 9741124	A1	19980319	AU 1997-41124	19970901
EP 929576	A1	19990721	EP 1997-938802	19970901
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
JP 2000517308	T2	20001226	JP 1998-511193	19970901
US 2002025933	A1	20020228	US 2001-908534	20010718

PRIORITY APPLN. INFO.:

DK 1996-931	A	19960830
DK 1996-1259	A	19961108
DK 1996-1470	A	19961220
US 1997-35905P	P	19970124
US 1997-36226P	P	19970125
JP 1998-511183	A3	19970822
WO 1997-DK360	W	19970901
US 1997-922200	B2	19970902
DK 1998-271	A	19980227
US 1998-85789P	P	19980518
US 1999-258187	B1	19990225

AB Derivs. of hGLP-2 (H-His-Ala-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Met-Asn-Thr-Ile-Leu-Asp-Asn-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-Lys-Ile-Thr-Asp-Arg-OH), where a lipophilic substituent (such as an acyl group of a straight-chain or branched fatty acid) is attached to any one amino acid residue, are claimed. For example, Lys30(N.epsilon.-tetradecanoyl)hGLP-2 was synthesized in 47% yield from the reactants hGLP-2 and tetradecanoic acid hydroxysuccinimide ester in the presence of N-ethyl-N,N-diisopropylamine (EDPA) and N-methyl-2-pyrrolidone (NMP). The titled compds. can be used in the treatment of obesity, small bowel syndrome, etc. (no data).

L11 ANSWER 3 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 96042491 MEDLINE
DOCUMENT NUMBER: 96042491 PubMed ID: 7588223
TITLE: Regulation of insulin release by phospholipase C activation in mouse islets: differential effects of glucose and neurohumoral stimulation.
AUTHOR: Zawalich W S; Zawalich K C; Kelley G G
CORPORATE SOURCE: Yale University School of Nursing, New Haven, Connecticut

06536-0740, USA.
CONTRACT NUMBER: 02089
41230
45735
SOURCE: ENDOCRINOLOGY, (1995 Nov) 136 (11) 4903-9.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951127

AB Rat islets respond to glucose stimulation with a marked first and second phase increase in insulin secretion. In contrast, mouse islets have a similar first phase response but little second phase secretion. In these studies, we determined if activation of phospholipase C (PLC) accounts for these differences in second phase insulin secretion in these two species. Stimulation of freshly isolated mouse and rat islets with 15 mM glucose resulted in comparable first phase insulin secretion; however, the second phase response from mouse islets was only doubled from 28 +/- 6 to 60 +/- 7 pg/islet.min compared with an increase from 24 +/- 4 to 1064 +/- 93 pg/islet.min from rat islets. The addition of the muscarinic agonist carbachol (100 microM) in the presence of 15 mM glucose, however, markedly increased second phase insulin release from mouse islets to 801 +/- 80 pg/islet.min. Similar increases in second phase insulin release from mouse islets were obtained with the addition of 500 nM of the protein kinase C activator ***tetradecanoyl*** phorbol acetate in the presence of 15 mM glucose. However, the incretin factor ***glucagon*** - ***like*** ***peptide*** -1, which elevates islet cAMP levels, had little effect on second phase insulin release in the mouse. An analysis of PLC-mediated phosphoinositide (PI) hydrolysis revealed that 15 mM glucose increased inositol phosphate (IP) accumulation 0.5-fold above baseline in mouse islets compared with 3.7-fold in rat islets. In contrast, carbachol stimulated IP accumulation 3.5-fold in both mouse and rat islets. Analysis of PLC isozymes with isozyme specific monoclonal antibodies, demonstrated that mouse islets express 14 +/- 4% of PLC-delta 1 and 18 +/- 6% of PLC-beta 1 compared with rat islets but similar amounts of the PLC-gamma 1 (117 +/- 16%). These findings suggest that the decreased second phase insulin secretory response in mouse compared with rat islets results, at least in part, from an inability of high glucose to stimulate comparable increments in PI hydrolysis. This lack of glucose responsiveness may be due to the pronounced underexpression of specific PLC isozymes in the mouse.

L11 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:290473 CAPLUS
DOCUMENT NUMBER: 120:290473
TITLE: Stimulation of glucagon-like peptide-1 secretion by muscarinic agonist in a murine intestinal endocrine cell line
AUTHOR(S): Abello, Jacques; Ye, Fei; Bosshard, Arlette; Bernard, Christine; Cuber, Jean Claude; Chayvialle, Jean Alain
CORPORATE SOURCE: Hop. Edouard Herriot, Lyon, 69437, Fr.
SOURCE: Endocrinology (1994), 134(5), 2011-17
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies on the cholinergic regulation of intestinal L-cells have been focused on the release of enteroglucagon, but the signal transduction pathways were not defined. These were here investigated by using as index the release of immunoreactive ***glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) from the endocrine cell line STC-1, that has been shown to contain proglucagon mRNA transcripts. Abundant ***GLP*** - ***1*** immunoreactivity was revealed in STC-1 cells at immunocytochem. and by RIA. The cell content was 4927 pg/106 cells, as measured with antiserum 199D that recognizes specifically the C-terminal amidated forms of ***GLP*** - ***1*** . The secretion of ***GLP*** - ***1*** over a 2-h incubation period amounted to 1.4% of the total ***GLP*** - ***1*** cell content and was increased by 10 .mu.m forskolin and 100 nm 12-O- ***tetradecanoyl*** phorbol 13-acetate

to 206% and 574% of control values, resp. The cholinergic agonist carbachol stimulated ***GL* - ***1*** secretion in a concn.-dependent manner; maximal release was obsd. at 1 mM carbachol (228% of the control value). Binding of the muscarinic antagonist [N-methyl-3H]scopolamine ([3H]NMS) on cell homogenates was time dependent, specific, and saturable. Scatchard anal. revealed 1 class of receptors (Kd, 14 pM; binding capacity, 20 fmol/mg protein). Carbachol (0.1 .mu.m to 1 mM) dose dependently displaced [3H]NMS binding and increased the intracellular Ca concn. without modification of adenylate cyclase activity. The order of potency of different antagonists, showing a preferential affinity for M1, M2, and M3 muscarinic receptor subtypes, to inhibit [3H]NMS binding, the carbachol-induced increase in intracellular Ca, and carbachol-stimulated ***GLP*** - ***1*** secretion, was as follows: atropine (nonselective) > 4-diphenylacetoxy-N-methylpiperidine methiodide (M3) > pirenzepine (M1) > AF-DX 116 (M2). Evidently, secretion of ***GLP*** - ***1*** induced by cholinergic agonist depends on muscarinic M3-subtype receptors in the endocrine intestinal cell line STC-1. This system may prove useful to study the cellular mechanisms of ***GLP*** - ***1*** secretion.

=> d his

(FILE 'HOME' ENTERED AT 07:57:13 ON 21 MAY 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 07:57:48 ON 21 MAY 2002

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L1          9389 S (GLUCAGON-LIKE PEPTIDE) OR GLP-1 OR GLP-2
L2        730112 S LIPOPHILIC OR (FATTY ACID)
L3           322 S L1 (P) L2
L4            13 S L3 (P) SUBSTIT?
L5             8 DUPLICATE REMOVE L4 (5 DUPLICATES REMOVED)
L6       1567656 S SPACER OR LINK?
L7        221176 S (SUCCINIC ACID) OR GLU OR ASP OR LYS OR GLY-LYS
L8         15810 S L6 (P) L7
L9         13606 S TETRADECANOYL
L10            8 S L1 (P) L9
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L12            4 S L11 NOT L5
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L13 30 L3 AND L6

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KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L13
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L15 12 L14 NOT (L5 OR L11)

=> d l15 1-12 ibib abs

L15 ANSWER 1 OF 12 MEDLINE
ACCESSION NUMBER: 1999335761 MEDLINE
DOCUMENT NUMBER: 99335761 PubMed ID: 10395622
TITLE: Biochemical basis of oligofructose-induced hypolipidemia in animal models.
AUTHOR: Delzenne N M; Kok N N
CORPORATE SOURCE: Unite de Biochimie Toxicologique et Cancerologique, Universite Catholique de Louvain, UCL-PMNT 7369-B-1200 Brussels, Belgium.
SOURCE: JOURNAL OF NUTRITION, (1999 Jul) 129 (7 Suppl) 1467S-70S. Journal code: JEV; 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820

Entered Medline: 19990812

AB Oligofructose (OFS), a mixture of nondigestible/fermentable fructooligosaccharides, decreases serum triacylglycerol (TAG) when it is included in the standard, fiber-free or high fat diet of rats. This paper summarizes in vivo and in vitro data to establish a biochemical mechanism underlying the hypolipidemic effect of OFS. When OFS is added to the standard (carbohydrate-rich) diet of rats at the dose of 10 g/100 g, a TAG-lowering action occurs as a consequence of a reduction of de novo liver ***fatty*** ***acid*** synthesis. The depression in the activity of all lipogenic enzymes and ***fatty*** ***acid*** synthase mRNA suggests that OFS modifies the gene expression of lipogenic enzymes. Through its modulation of de novo lipogenesis, OFS can protect against liver lipid accumulation induced by providing 10% fructose-enriched water for 48 h. OFS also significantly decreases serum insulin and glucose, which are both known to participate in the nutritional regulation of lipogenesis. It also increases the intestinal production of incretins, namely, glucose-dependent insulinotropic peptide and ***glucagon*** - ***like*** ***peptide*** 1. This latter phenomenon results mainly from promotion of intestinal tissue proliferation by oligofructose fermentation end-products. Collectively, a ***link*** likely exists between the modulation of hormone and incretin production by OFS, and its antilipogenic effect.

L15 ANSWER 2 OF 12 MEDLINE

ACCESSION NUMBER: 1999265489 MEDLINE
DOCUMENT NUMBER: 99265489 PubMed ID: 10334320
TITLE: A sib-pair analysis study of 15 candidate genes in French families with morbid obesity: indication for ***linkage*** with islet 1 locus on chromosome 5q.
AUTHOR: Clement K; Dina C; Basdevant A; Chastang N; Pelloux V; Lahlou N; Berlan M; Langin D; Guy-Grand B; Froguel P
CORPORATE SOURCE: Nutrition Department, Hotel-Dieu Hospital, Paris, France.
SOURCE: DIABETES, (1999 Feb) 48 (2) 398-402.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 20000303
Entered Medline: 19990610

AB As part of an ongoing search for susceptibility genes in obese families, we performed ***linkage*** analyses in 101 French families between qualitative and quantitative traits related to morbid obesity and polymorphisms located in or near 15 candidate genes whose products are involved in body weight regulation. These included cholecystokinin A and B receptors (CCK-AR and CCK-BR), ***glucagon*** - ***like*** ***peptide*** 1 receptor (GLP-1R), the LIM/homeodomain islet-1 gene (Isl-1), the caudal-type homeodomain 3 (CDX-3), the uncoupling protein 1 (UCP-1), the beta3-adrenoceptor (beta3-AR), the ***fatty*** ***acid*** -binding protein 2 (FABP-2), the hormone-sensitive lipase (HSL), the lipoprotein lipase (LPL), the apoprotein-C2 (apo-C2), the insulin receptor substrate-1 (IRS-1), the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), tumor necrosis factor-alpha (TNF-alpha), and the liver carnitine palmitoyltransferase-1 (CPT-1). Phenotypes related to obesity such as BMI, adult life body weight gain, fasting leptin, insulin, fasting glycerol, and free ***fatty*** ***acids*** were used for nonparametric sib-pair analyses. A weak indication for ***linkage*** was obtained between the Isl-1 locus and obesity status defined by a z score over one SD of BMI (n = 226 sib pairs, pi = 0.54 +/- 0.02, P = 0.03). Moreover, a suggestive indication for ***linkage*** was found between the Isl-1 locus and BMI and leptin values (P = 0.001 and 0.0003, respectively) and leptin adjusted for BMI (P = 0.0001). Multipoint analyses for leptin trait with Isl-1 and two flanking markers (D5S418 and D5S407) showed that the logarithm of odds (LOD) score is 1.73, coinciding with the Isl-1 locus. Although marginally positive indications for ***linkage*** in subgroups of families were found with IRS-1, CPT-1, and HSL loci, our data suggested that these genes are not major contributors to obesity. Whether an obesity susceptibility gene (Isl-1 itself or another nearby gene) lies on chromosome 5q should be determined by further analyses.

L15 ANSWER 3 OF 12 MEDLINE
ACCESSION NUMBER: 1999017745 MEDLINE
DOCUMENT NUMBER: 99017745 PubMed ID: 9802745
TITLE: Influence of glucagon-like peptide 1 on fasting glycemia in type 2 diabetic patients treated with insulin after sulfonylurea secondary failure.
AUTHOR: Nauck M A; Sauerwald A; Ritzel R; Holst J J; Schmiegel W
CORPORATE SOURCE: Department of Medicine, Ruhr-University, Knappschafts-Krankenhaus, Bochum, Germany.
SOURCE: DIABETES CARE, (1998 Nov) 21 (11) 1925-31.
Journal code: EAG; 7805975. ISSN: 0149-5992.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990114

AB OBJECTIVE: ***Glucagon*** - ***like*** ***peptide*** 1 (***GLP*** - ***1***) has glucose-dependent insulinotropic and glucagonostatic actions in type 2 diabetic patients on diet and on oral agents. It is not known, however, whether after secondary sulfonylurea failure, ***GLP*** - ***1*** is still effective. RESEARCH DESIGN AND METHODS: Therefore, 10 type 2 diabetic patients (6 women, 4 men; age 65+/-10 years, BMI 30.4+/-5.1 kg/m2, HbA1c 8.2+/-1.5%, 6+/-3 [2-13] years after starting insulin treatment) were examined in the fasting state after discontinuing NPH insulin on the evening before the two study days. ***GLP*** - ***1*** (1.2 pmol x kg(-1) x min(-1) or placebo (NaCl with 1% human serum albumin) were infused over 6 h. Plasma glucose (glucose oxidase) insulin (IMx), and C-peptide (enzyme- ***linked*** immunosorbent assay) were measured. Statistical analysis was performed using repeated measures analysis of variance. RESULTS: Fasting plasma glucose was 9.4+/-0.5 mmol/l and was reduced by ***GLP*** - ***1*** to 5.3+/-0.3 (3.9-7.3) mmol/l (placebo: 8.2+/-0.7 mmol/l; P < 0.0001). ***GLP*** - ***1*** transiently increased insulin (from 115+/-31 to 222+/-64 pmol/l at 150 min; P < 0.0001) and C-peptide (from 1.00+/-0.12 to 1.90+/-0.23 nmol/l at 120 min; P < 0.0001) with no effect of placebo. Glucagon and free ***fatty*** ***acids*** were lowered transiently. After normalization of plasma glucose, insulin and C-peptide concentrations became lower again during the ongoing administration of exogenous ***GLP*** - ***1*** , and no hypoglycemia occurred. CONCLUSIONS: It is concluded that exogenous ***GLP*** - ***1*** effectively lowers plasma glucose concentrations in advanced type 2 diabetes long after sulfonylurea secondary failure. These findings may broaden the applicability of ***GLP*** - ***1*** -derived drugs as a new treatment to nearly all type 2 diabetic patients.

L15 ANSWER 4 OF 12 MEDLINE
ACCESSION NUMBER: 97309265 MEDLINE
DOCUMENT NUMBER: 97309265 PubMed ID: 9166680
TITLE: Genetics of NIDDM in France: studies with 19 candidate genes in affected sib pairs.
AUTHOR: Vionnet N; Hani E H; Lesage S; Philippi A; Hager J; Varret M; Stoffel M; Tanizawa Y; Chiu K C; Glaser B; Permutt M A; Passa P; Demenais F; Froguel P
CORPORATE SOURCE: Centre National Recherche Scientifique, Institut Pasteur de Lille, France.. n.vionnet@xenope.univ-lille2.fr
CONTRACT NUMBER: 1-P41-RR-03655 (NCRR)
DK-16746 (NIDDK)
SOURCE: DIABETES, (1997 Jun) 46 (6) 1062-8.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630

Entered Medline: 19970619

AB As part of an ongoing search for susceptibility loci for NIDDM we tested 19 genes whose products are implicated in insulin secretion or action for ***linkage*** with NIDDM. Loci included the G-protein-coupled inwardly rectifying potassium channels expressed in beta-cells (KCNJ3 and KCNJ7), glucagon (GCG), glucokinase regulatory protein (GCKR), ***glucagon*** -***like*** ***peptide*** I receptor (GLP1R), LIM/homeodomain islet-1 (ISL1), caudal-type homeodomain 3 (CDX3), proprotein convertase 2 (PCSK2), cholecystokinin B receptor (CCKBR), hexokinase 1 (HK1), hexokinase 2 (HK2), mitochondrial FAD-glycerophosphate dehydrogenase (GPD2), liver and muscle forms of pyruvate kinase (PKL, PKM), ***fatty*** ***acid*** -binding protein 2 (FABP2), hepatic phosphofructokinase (PFKL), protein serine/threonine phosphatase 1 beta (PPP1CB), and low-density lipoprotein receptor (LDLR). Additionally, we tested the histidine-rich calcium locus (HRC) on chromosome 19q. All regions were tested for ***linkage*** with microsatellite markers in 751 individuals from 172 families with at least two patients with overt NIDDM (according to World Health Organization criteria) in the sibship, using nonparametric methods. These 172 families comprise 352 possible affected sib pairs with overt NIDDM or 621 possible affected sib pairs defined as having a fasting plasma glucose value of >6.1 mmol/l or a glucose value of >7.8 mmol/l 2 h after oral glucose load. No evidence for ***linkage*** was found with any of the 19 candidate genes and NIDDM in our population by nonparametric methods, suggesting that those genes are not major contributors to the pathogenesis of NIDDM. However, some evidence for suggestive ***linkage*** was found between a more severe form of NIDDM, defined as overt NIDDM diagnosed before 45 years of age, and the CCKBR locus (11p15.4; P = 0.004). Analyses of six additional markers spanning 27 cM on chromosome 11p confirmed the suggestive ***linkage*** in this region. Whether an NIDDM susceptibility gene lies on chromosome 11p in our population must be determined by further analyses.

L15 ANSWER 5 OF 12 MEDLINE
ACCESSION NUMBER: 94148146 MEDLINE
DOCUMENT NUMBER: 94148146 PubMed ID: 7508874
TITLE: Search for a third susceptibility gene for maturity-onset diabetes of the young. Studies with eleven candidate genes.
AUTHOR: Vaxillaire M; Vionnet N; Vigouroux C; Sun F; Espinosa R 3rd; Lebeau M M; Stoffel M; Lehto M; Beckmann J S; Detheux M; +
CORPORATE SOURCE: Human Polymorphism Study Center, Paris, France.
CONTRACT NUMBER: CA-41644 (NCI)
DK-16746 (NIDDK)
DK-20595 (NIDDK)
SOURCE: DIABETES, (1994 Mar) 43 (3) 389-95.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19960129
Entered Medline: 19940322

AB Maturity-onset diabetes of the young (MODY) is a model for genetic studies of non-insulin-dependent diabetes mellitus. We have identified 15 MODY families in which diabetes is not the result of mutations in the glucokinase gene. This cohort of families will be useful for identifying other diabetes-susceptibility genes. Nine other candidate genes potentially implicated in insulin secretion or insulin action have been tested for ***linkage*** with MODY in these families, including glucokinase regulatory protein, hexokinase II, insulin receptor substrate 1, ***fatty*** ***acid*** -binding protein 2, ***glucagon*** -***like*** ***peptide*** -1 receptor, apolipoprotein C-II, glycogen synthase, adenosine deaminase (a marker for the MODY gene on chromosome 20), and phosphoenolpyruvate carboxykinase. None of these loci showed evidence for ***linkage*** with MODY, implying that mutations in these genes do not make a major genetic contribution to the development of MODY. In addition to these ***linkage*** analyses, one or two affected subjects from each family were screened for the presence of the A to G mutation at nucleotide 3,243 of the mitochondrial tRNA(Leu(UUR)) gene. This mutation was not found in any of these subjects. Finally, we report

the localization of the gene encoding the regulatory protein of glucokinase to chromosome 2, and p22.3 and the identification of a restriction fragment length polymorphism at this locus.

L15 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:824465 CAPLUS
TITLE: GLP-1 derivatives as novel compounds for the treatment of type 2 diabetes: Selection of NN2211 for clinical development
AUTHOR(S): Knudsen, L. Bjerre; Agerso, H.; Bjenning, C.; Bregenholt, S.; Carr, R. D.; Godtfredsen, C.; Holst, J. J.; Huusfeldt, P. O.; Larsen, M. O.; Larsen, P. J.; Nielsen, P. F.; Ribel, U.; Rolin, B.; Romer, J.; Sturis, J.; Wilken, M.; Kristensen, P.
CORPORATE SOURCE: Novo Nordisk, Maaloev, DK-2760, Den.
SOURCE: Drugs of the Future (2001), 26(7), 677-685
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review describes the biol. aspects of ***Glucagon*** - ***like*** ***peptide*** -1 (***GLP*** - ***1***) and provides a detailed description of a series of ***GLP*** - ***1*** derivs. designed for once-daily administration. ***GLP*** - ***1*** compds. form a new class of drugs in clin. development for the treatment of type 2 diabetes. The peptide hormone ***GLP*** - ***1*** could be derivatized almost anywhere in the C-terminal part of the peptide and that derivatization with both short and long ***fatty*** ***acids*** and amino acid-derived ***spacers*** resulted in compds. that were highly potent. NN2211 is a metabolically stable compd. with potency equal to ***GLP*** - ***1*** . It has been demonstrated to lower blood glucose and body wt., and to increase or maintain .beta.-cell mass.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:684245 CAPLUS
DOCUMENT NUMBER: 134:85382
TITLE: Modulation of gastrointestinal incretin hormones with dietary fiber and the management of non-insulin dependent diabetes mellitus
AUTHOR(S): McBurney, M. I.
CORPORATE SOURCE: Nutrition and Metabolism Research Group, Departments of Agricultural, Food and Nutritional Science and Medicine, University of Alberta, Edmonton, AB, T6G 2P5, Can.
SOURCE: From Nutritional Science to Nutrition Practice for Better Global Health, Proceedings of the International Congress of Nutrition, 16th, Montreal, QC, Canada, July, 1997 (1998), Meeting Date 1997, 40-41. Editor(s): Fitzpatrick, D. W.; Anderson, J. E.; L'Abbe, M. L. Canadian Federation of Biological Societies: Ottawa, Ont.
CODEN: 69AKK9
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 27 refs. The topics include ***link*** of dietary carbohydrates and fiber to insulin secretion regulation and non-insulin dependent diabetes mellitus (NIDDM), regulatory roles of the peptide hormone incretin, glucose-dependent insulinotropic polypeptide and ***glucagon*** - ***like*** ***peptides*** 1 and 2 produced by gastrointestinal mucosal cells, and dietary fiber and produced volatile ***fatty*** ***acids*** interactions with the secretion of these hormones.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:424067 CAPLUS
DOCUMENT NUMBER: 131:184337
TITLE: Biochemical basis of oligofructose-induced hypolipidemia in animal models

AUTHOR(S): Delzenne, Nathalie M.; Kok, Nadine N.
CORPORATE SOURCE: Unite de [redacted]ochimie Toxicologique et Cance[redacted]logique, Universite Catholique de Louvain, UCL-PMNT 7369, Brussels, B-1200, Belg.
SOURCE: Journal of Nutrition (1999), 129(7S), 1467S-1470S
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oligofructose (OF, Raftilose P95), a mixt. of nondigestible/fermentable fructooligosaccharides, decreases blood serum triacylglycerol (TAG) levels when it is included in the std. fiber-free or high-fat diet of rats. This paper summarizes in vivo and in vitro data to establish a biochem. mechanism underlying the hypolipidemic effect of OF. When OF was added to the std. carbohydrate-rich diet of rats at 10 g/100 g feed, the TAG-lowering action was a consequence of decreased de novo liver ***fatty*** ***acid*** synthesis. The depression in the activity of all lipogenic enzymes and ***fatty*** ***acid*** synthase mRNA suggested that OF modified gene expression of lipogenic enzymes. Through the modulation of de novo lipogenesis, OF can protect against liver lipid accumulation induced by providing 10% fructose-enriched water for 48 h. OF also decreased blood serum insulin and glucose levels which participate in the nutritional regulation of lipogenesis. OF also increased the intestinal prodn. of incretins (glucose-dependent insulinotropic peptide and ***glucagon*** - ***like*** ***peptide*** 1). This latter phenomenon resulted mainly from the promotion of intestinal tissue proliferation by oligofructose fermn. end products. There is a likely ***link*** between the OF modulation of hormone and incretin prodn. and its antilipogenic effect.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999227036 EMBASE
TITLE: On the pathophysiology of late onset non-insulin dependent diabetes mellitus: Current controversies and new insights.
AUTHOR: Vaag A.
CORPORATE SOURCE: A. Vaag, Forarsvej 17, DK-2920 Charlottenlund, Denmark
SOURCE: Danish Medical Bulletin, (1999) 46/3 (197-234).
Refs: 554
ISSN: 0907-8916 CODEN: DMBUAE
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The development of late onset non-insulin dependent diabetes mellitus (NIDDM) is due to a complicated interplay between genes and environment on one-side, and the interaction between metabolic defects in various tissues including the pancreatic beta cell (decreased insulin secretion), skeletal muscle (insulin resistance), liver (increased gluconeogenesis), adipose tissue (increased lipolysis) and possibly gut incretin hormones (defective ***glucagon*** ***like*** ***peptide*** 1 (GLP1) secretion) on the other side. Evidence for a genetic component includes the finding of a variety of metabolic defects in various tissues in non-diabetic subjects with a genetic predisposition to NIDDM, higher concordance rates for abnormal glucose tolerance including NIDDM in monozygotic compared with dizygotic twins, and the more recent demonstration of different NIDDM susceptibility genes at the sites of Insulin Receptor Substrate 1 (IRS1), the beta-3 adrenergic receptor, and the sulfonylurea receptor. However, the latter susceptibility genes only explain a minor proportion of NIDDM in the general population, and the quantitative extent to which genetic versus non-genetic factors contribute to NIDDM is presently unsolved. Environmental components include both an early intrauterine component associated with low birth weight, and later postnatal components including low physical activity, high fat diet, and the subsequent development of obesity and elevated plasma and tissue free ***fatty*** ***acid*** levels. Our finding of lower birth weights in monozygotic twins compared with their non-diabetic genetically identical co-twins excludes the possibility that the association between NIDDM and low birth weight as demonstrated in several studies may solely be explained by a coincidence

between a certain gene causing both a low birth weight and an increased risk of NIDDM. Young first degree relatives of patients with NIDDM are characterized by hyperinsulinaemia and peripheral insulin resistance, which in turn may be explained by a decreased insulin activation of the enzyme glycogen synthase in skeletal muscle. Therefore, a defective skeletal muscle glycogen synthase activation may represent an early phenotypic expression of a genetic defect contributing to an increased risk of later development of NIDDM. However, elderly insulin resistant non-diabetic co-twins (64 years old) of twins with overt NIDDM does not - in contrast to their NIDDM co-twins - have a significantly decreased insulin activation of glycogen synthase in skeletal muscle. This demonstrates that the defective muscle glycogen synthase insulin activation has an apparent non-genetic component, and that this key defect of metabolism can be escaped or postponed even in non-diabetic subjects with a presumeably 100% genetic predisposition to NIDDM. The insulin activation of glycogen synthase in skeletal muscle is compensated or apparently normalised in NIDDM patients when studied during their ambient fasting hyperglycaemia and a subsequent isoglycaemic (hyperglycaemic) physiologic insulin infusion. This indicates that the prevailing hyperglycaemia in NIDDM subjects compensates for the defective insulin activation of glycogen synthase present in those subjects when studied during eulycaemia. Our data and those of others also indicates that hyperglycaemia in NIDDM compensates for the defects in insulin secretion, the disproportionately elevated hepatic glucose production, and to some extent for the increased lipid oxidation and the decreased glucose oxidation present in NIDDM patients. Accordingly, NIDDM subjects exhibit all of those defects of metabolism when studied during 'experimental decompensation' when the ambient hyperglycaemia is normalized by a prior and later withdrawn intravenous insulin infusion. However, shortly after the withdrawal of the intravenous insulin infusion, the plasma glucose concentration increased spontaneously in the NIDDM patients. This was primarily due to an increased hepatic glucose production in the presence of a normal or slightly increased peripheral glucose uptake, glucose storage rate and skeletal muscle glycogen synthase activity. The data indicated a role for both the glucose ***fatty*** ***acid*** cycle and the Cori cycle for the spontaneously increasing plasma glucose concentration after decompensation in NIDDM patients. While young first degree relatives of patients with NIDDM exhibit insulin resistance and hyperinsulinaemia, the major defect of metabolism present in elderly monozygotic non-diabetic co-twins of NIDDM twins is a defective insulin secretion, when expressed either in absolute terms, or when related to the slightly impaired insulin action present in those subjects. Our data, and those of others, therefore suggest a major impact of a possibly genetically determined age dependent decline in beta cell function for the subsequent development of NIDDM in genetically predisposed individuals. However, the twin data also demonstrates the presence of a secondary non-genetic component of the defective insulin secretion in NIDDM subjects. A slightly reduced GLP1 secretion may contribute to the secondary defect of insulin secretion in NIDDM during oral glucose ingestion. However, there is no evidence that impaired gut incretin hormone secretion contributes to the defective insulin secretion in nondiabetic genetically predisposed individuals. The metabolic factors responsible for the secondary defects of metabolism in NIDDM primarily involve hyperglycaemia itself through the concept of 'glucose toxicity', and elevated plasma and tissue free ***fatty*** ***acid*** levels partly via the 'glucose- ***fatty*** ***acid*** cycle'. Evidence for the role of the glucose ***fatty*** ***acid*** cycle in NIDDM include partial reversibility of the defects of insulin action and hepatic glucose production, together with the lowering of plasma glucose concentration, in NIDDM patients after acute administration of the antilipolytic drug acipimox.

L15 ANSWER 10 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:121690 SCISEARCH
THE GENUINE ARTICLE: 396RD
TITLE: Central role of the adipocyte in the metabolic syndrome
AUTHOR: Bergman R N (Reprint); Van Citters G W; Mittelman S D; Dea M K; Hamilton-Wessler M; Kim S P; Ellmerer M
CORPORATE SOURCE: Keck USC, Sch Med, Dept Physiol & Biophys, Los Angeles, CA 90033 USA (Reprint); Univ So Calif, Diabet Res Ctr, Los Angeles, CA 90033 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF INVESTIGATIVE MEDICINE, (JAN 2001) Vol. 49, No.

1, pp. 119-126.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 1081-5589.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Insulin resistance is associated with a plethora of chronic illnesses, including Type 2 diabetes, dyslipidemia, clotting dysfunction, and colon cancer. The relationship between obesity and insulin resistance is well established, and an increase in obesity in Western countries is implicated in increased incidence of diabetes and other diseases. Central, or visceral, adiposity has been particularly associated with insulin resistance; however, the mechanisms responsible for this association are unclear. Our laboratory has been studying the physiological mechanisms relating visceral adiposity and insulin resistance. Moderate fat feeding of the dog yields a model reminiscent of the metabolic syndrome, including visceral adiposity, hyperinsulinemia, and insulin resistance. We propose that insulin resistance of the liver derives from a relative increase in the delivery of free ***fatty*** ***acids*** (FFA) from the omental fat depot to the liver (via the portal vein). Increased delivery results front 1) more stored lipids in omental depot, 2) severe insulin resistance of the central fat depot, and 3) possible regulation of visceral lipolysis by the central nervous system. The significance of portal FFA delivery results from the importance of FFA in the control of liver glucose production. Insulin regulates liver glucose output primarily via control of;adipocyte lipolysis. Thus, because FFA regulate the liver, it is expected that visceral adiposity will enhance delivery of FFA to the liver and make the liver relatively insulin resistant. It is of interest how the intact organism compensates for insulin resistance secondary to visceral fat deposition. While part of the compensation is enhanced B-cell sensitivity to glucose, an equally important component is reduced liver insulin clearance, which shows for a greater fraction of B-cell insulin secretion to bypass liver degradation, to enter the systemic circulation, and to result in hyperinsulinemic compensation. The signal(s) resulting in B-cell up-regulation and reduced liver insulin clearance with visceral adiposity is (are) unknown, but it appears that the ***glucagon*** - ***like*** ***peptide*** (***GLP*** - ***1***) hormone plays an important role. The integrated response of the organism to central adiposity is complex, involving several organs and tissue beds. An investigation into the integrated response may help to explain the features of the metabolic syndrome.

L15 ANSWER 11 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 97:712420 SCISEARCH
THE GENUINE ARTICLE: XW882
TITLE: Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes
AUTHOR: DeFronzo R A (Reprint)
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, DEPT MED, DIV DIABET, 7703 FLOYD CURL DR, SAN ANTONIO, TX 78284 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: DIABETES REVIEWS, (SEP-OCT 1997) Vol. 5, No. 3, pp. 177-269.
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314.
ISSN: 1066-9442.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 878

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Individuals with type 2 diabetes are characterized by abnormalities in insulin action and insulin secretion, However, despite intensive investigation, the genes responsible for the insulin resistance and impaired insulin secretion remain undefined. The candidate-gene approach has failed to identify any specific gene or combination of genes that can account for even a minority of adult cases of type 2 diabetes. Although a number of laboratories have initiated genomewide searches to identify potential susceptibility loci for type 2 diabetes, consistent and reproducible ***linkage*** to satellite markers has yet to emerge. It

has beers suggested that a more precise definition of the diabetic phenotype may prove useful in delineating diabetogenic genes. This review provides an in-depth discussion of established metabolic, biochemical, and molecular abnormalities responsible for type 2 diabetes. It is anticipated that this discussion will establish a framework for the identification of additional candidate genes that need to be examined and provide a sound scientific basis for the more precise definition of the diabetic phenotype for use in future genomewide searches.

L15 ANSWER 12 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 93:381399 SCISEARCH
THE GENUINE ARTICLE: LG351
TITLE: DIETARY CARBOHYDRATE UTILIZATION IN COD (GADUS-MORHUA) - METABOLIC RESPONSES TO FEEDING AND FASTING
AUTHOR: HEMRE G I (Reprint); LIE O; SUNDBY A
CORPORATE SOURCE: DIRECTORATE FISHERIES, INST NUTR, STRANDGATEN 229, POB 1900, N-5024 BERGEN, NORWAY (Reprint); NORWEGIAN COLL VET MED, DEPT PHYSIOL & NUTR, N-0033 OSLO 1, NORWAY
COUNTRY OF AUTHOR: NORWAY
SOURCE: FISH PHYSIOLOGY AND BIOCHEMISTRY, (APR 1993) Vol. 10, No. 6, pp. 455-463.
ISSN: 0920-1742.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Moist diets with increasing amounts of carbohydrate (0.5%, 10% and 21% on a dry weight basis) were each fed to duplicate groups of cod (initial weight 370 g) for 8 weeks, after which all groups were fasted for 4 weeks. Protein energy was high and accounted for more than 70% of the gross energy content in all feeds, and the diets were maintained isocaloric by substituting lipid energy for carbohydrate energy. No indigestible binder was added. Excellent growth and feed conversion were obtained in all groups. After 4 weeks of fasting, fish previously fed diets with either 10% or 21% carbohydrate showed significantly higher weight loss than fish fed the diet without carbohydrate. Liver glycogen reached 10% of liver wet weight in fish fed diets containing 10% or 21% carbohydrate and 5% in fish receiving 0.5% carbohydrate after 8 weeks. Following 4 weeks of fasting, liver glycogen was reduced to similar levels in all fish. Plasma glucose levels 4 h after feeding were higher in fish fed the diets with 10% or 21% carbohydrate and plasma free amino acid levels (FAA) were lower, than in fish fed the diet containing 0.5% carbohydrate. Blood lactate concentrations were unaffected during the first 24 h after feeding. After 4 weeks of food deprivation, the levels were significantly reduced only in the 21% carbohydrate group. A ***link*** between glucagon and protein metabolism is suggested because plasma glucagon concentration followed the same pattern as the concentrations of plasma FAA throughout the study. Insulin and glucagon-like peptide (GLP) showed a covariation throughout the experiment. Reduced plasma insulin levels were seen after fasting concomitant with reduction in the levels of FAA and glucose. It is suggested that insulin secretion in cod is affected both by plasma FAA and glucose and that cod meets food deprivation by slowing down metabolism.

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(FILE 'HOME' ENTERED AT 07:57:13 ON 21 MAY 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 07:57:48 ON 21 MAY 2002

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L1          9389 S (GLUCAGON-LIKE PEPTIDE) OR GLP-1 OR GLP-2
L2        730112 S LIPOPHILIC OR (FATTY ACID)
L3           322 S L1 (P) L2
L4            13 S L3 (P) SUBSTIT?
L5             8 DUPLICATE REMOVE L4 (5 DUPLICATES REMOVED)
L6       1567656 S SPACER OR LINK?
L7        221176 S (SUCCINIC ACID) OR GLU OR ASP OR LYS OR GLY-LYS
L8         15810 S L6 (P) L7
L9         13606 S TETRADECANOYL
L10            8 S L1 (P) L9
L11            4 DUPLICATE REMOVE L10 L10\ (4 DUPLICATES REMOVED)
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L12             4 S L11 NOT L5
L13            30 S L3 AND L6
L14            12 DUPLICATE REMOVE L13 (18 DUPLICATES REMOVED)
L15            12 S L14 NOT (L5 OR L11)

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    94.41      94.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -7.43      -7.43

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